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Comparative analysis of overall survival in non-small cell lung cancer patients with and without different organ metastases

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Abstract:

Lung cancer is the leading cause of cancer death globally. Non-small cell lung cancer (NSCLC) constitutes more than 80% of all lung cancers, and patients with distant metastasis have much higher mortality. The survival times of NSCLC patients with metastasis have been reported in early studies, however, it remains unclear whether there are variations or patterns in survival times of patients with different metastases. Therefore, we assessed risk factors for distant metastases and the effects of different organ metastasis on overall survival (OS) in patients with NSCLC. Methods: demographics and clinical data of NSCLC patients with and without distant metastasis were collected from the Surveillance, Epidemiology, and End Result (SEER) database between 2010 and 2016. We investigated risk factors for distant metastasis patients and compared the difference in OS of NSCLC patients with different metastatic sites. Results: a total of 3849 patients diagnosed with NSCLC were screened from the SEER database with 41% (1577) of the patients having distant metastasis. During the follow-up period, 3221 (83.7%) patients died and, of all the deceased patients, 2935 (88.4%) died of lung cancer while only 286 (11.6%) died from other diseases or causes. The occurrence of distant metastasis was closely related to the patient's age, primary tumour site, tumour grade, T stage, N stage, surgery of primary site, radiation therapy, and chemotherapy ($p<0.05$). Compared to patients without metastasis, whose median OS was 13 months, the median OS of patients with metastasis was 6 months (lung), 5 months (liver), 5 months (bone), 4 months (brain), and 3 months (multiple organs). Conclusions: distant metastasis indicates a poor prognosis in NSCLC patients. There were significant differences in the prognosis of different metastatic sites and the order of their OS from high to low was: no metastasis > lung metastasis, liver metastasis, bone metastasis > brain metastasis, multiple organ metastasis.

Keywords: **metastasis, non-small cell lung cancer, overall survival, SEER.**

Classification number: **3.2**

Introduction

Lung cancer is a malignant tumour with the highest morbidity and mortality rates in the world for both men and women, which claims more lives than prostate, breast, and colon cancers combined [1]. Statistics from the Vietnam Ministry of Health show that lung cancer is the second leading cause of cancer death in Vietnam, and more than 20,000 new lung cancer patients are diagnosed across the country every year with up to 17,000 fatalities [2]. The age-standardised incidence rate for males is 40.2/100,000 while for women it is 10.6 per 100,000 people [2]. The 1-year survival rate of patients diagnosed with lung cancer is less than 50%, and over four-fifths of those die within 5 years of diagnosis [3]. According to histopathology, lung cancer has two major subtypes, namely, small cell lung cancer and NSCLC, with the latter constituting more than 80% of all lung cancers [4]. Despite noticeable advances in targeted therapy, the survival rates of NSCLC patients have not improved. Approximately 80% of all lung cancer patients have metastases in their lifetime, and once distant metastases occur, the 5-year survival rate drops to <5%, which indicates that metastasis has much higher mortality in NSCLC [5].

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The lung, liver, bone, and brain are common distant metastasis sites of NSCLC. While many studies have evaluated the survival time of NSCLC patients with metastasis to each of these organs, it remains unclear whether there is a difference in the survival times of each case. Therefore, the purpose of this study is to determine the risk factors for distant metastasis as well as the impact of metastasis in different organs on patient OS.

Materials and methods

Patient population and data collection

Patients were identified from the SEER database of the National Cancer Institute between 2010 and 2016. SEER*Stat Software 8.3.8 (National Cancer Institute, Bethesda, MD) was used to extract information from the SEER database.

The SEER database was developed by the National Cancer Institute and is supported by the Surveillance Research Program in the Division of Cancer Control and Population Science of the National Cancer Institute. This is one of the largest cancer epidemiological databases in the world and it collects information on demographic characteristics, clinical characteristics, and follow-up after diagnosis and treatment of cancer patients from 18 registries representing 28% of the US population. Researchers are granted permission to access this database for study after completing the registration and approval process.

Inclusion and exclusion criteria: among the NSCLC patients pathologically diagnosed from 2010 to 2016, patients with previous malignant tumours were excluded, and 21,985 cases were finally selected. We extracted the age, gender, race, marital status, pathology, degree of differentiation, surgery, T-staging, N-staging, survival time, radiation therapy, chemotherapy, metastasis site, etc., of each patient from the database. Pathological staging was based on American Joint Committee on Cancer (AJCC) 6th edition staging.

The inclusion criteria were as follows: (1) NSCLC patients diagnosed between 2010 and 2016; (2) patients with complete baseline and treatment information; and (3) patients with a complete follow-up and known survival time. The exclusion criteria were as follows: (1) more than one primary tumour; (2) unknown site and grade of primary neoplasm; (3) unknown N stage or T stage; (4) incomplete therapy information, which includes primary tumour surgery, radiation therapy, and chemotherapy; (5) unknown survival time; and (6) lack of metastasis information.

Grouping: the extracted NSCLC patients were divided into two groups. The NSCLC patients who did not have metastasis between 2010 and 2016 were placed into the non-metastasis group and the patients who had distant metastases during or after NSCLC was diagnosed from 2010 to 2016 were divided into the metastasis group.

We further divided the patients in the metastasis group into 5 subgroups based on the location of metastasis including the brain metastasis subgroup, bone metastasis subgroup, liver metastasis subgroup, lung metastasis subgroup, and multi-organ metastasis subgroup.

Demographics and clinical characteristics

Demographic characteristics of patients included age at diagnosis, sex, and marital status. To facilitate the evaluation and comparison, we converted the age of patients when diagnosed from a measurement variable into an ordinal categorical variable (≤60, 61-70, 71-80, and >80 years old). Marital status was characterised as married, unmarried, or unknown. It should be noted that the unmarried status included single or never married, separated, divorced, widowed, and domestic partner.

Clinical characteristics included primary tumour site, tumour grade, T and N stage, primary tumour surgery, chemotherapy, and radiation therapy. The primary tumour site was classified as main bronchus, upper lobe, middle lobe, lower lobe, or overlapping lesion of lung. There are 4 different types of tumour grades, which are grade I, grade II, grade III, and grade IV representing well differentiated, moderately differentiated, poorly differentiated, and undifferentiated, respectively. The tumour grade assists clinicians with determining how aberrant cancer cells and tissue appear under a microscope, as well as how rapidly cancer cells are expected to develop and spread. Low-grade cancer cells have a more natural appearance than high-grade cancer cells and develop and spread more slowly. T stage and N stage are based on the 7th edition of the AJCC. Regarding radiation therapy and chemotherapy, whether these were given preoperatively or postoperatively are both considered for NSCLC patients.

The survival time in this study is understood as the OS time, which was the period beginning from the time the patient was diagnosed to the time the patient died from

any cause. Follow-up was conducted at regular follow-up visits and/or through tele-communication.

Statistical analysis

The software SPSS 25.0 (Statistical Package for the Social Sciences, IBM Corporation, Armonk, NY, USA) was used for all statistical analyses in this study. Regarding the differences between groups and subgroups, a Chi-squared test was used to evaluate the categorical variables and the Log-rank test was used for the difference test of OS. The fraction of patient survival after treatment was measured by using the Kaplan-Meier estimator. A statistical test was considered statistically significant if its corresponding two-tailed P-value was less than 0.05.

Ethical considerations

The SEER database is an open-access database, hence, after signing the Data Use Agreement for the SEER 1975-2016 Research Data, we were allowed to access to the database to abstract the data. Thus, we did not need to acquire patients' informed consent or an ethical review committee statement.

Results

Characteristics of metastasis in NSCLC patients

As shown in the study design flowchart (Fig. 1), 21,985 patients diagnosed with NSCLC from January 2010 to December 2016 were initially identified. Based on the criteria outlined above, 18,136 ineligible patients were excluded, and a total of 3,849 patients remained both with and without distant metastases.

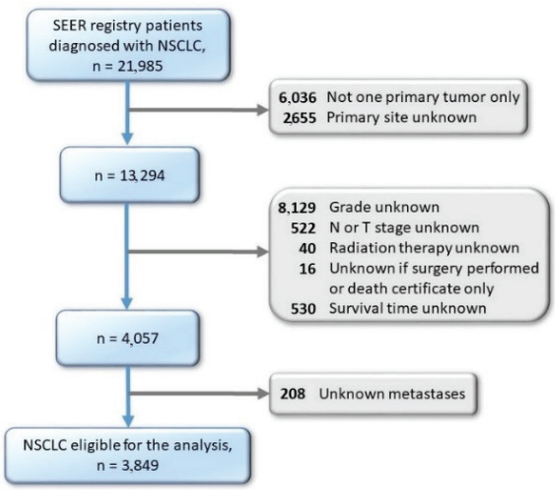

Fig. 1. Study design flowchart of the specific patient screening process.

There were a total of 1,577 out of 3,849 NSCLC patients with distant metastasis, which accounts for approximately 41.0%. The organ with the most cancer metastasis is bone (n=713), followed by brain (n=664), lung (n=563), and liver (n=349). Details of the number of patients with or without metastases are shown in Fig. 2. Among patients with metastasis, up to 561 patients had metastatic conditions in more than one organ making the rate more than one-third.

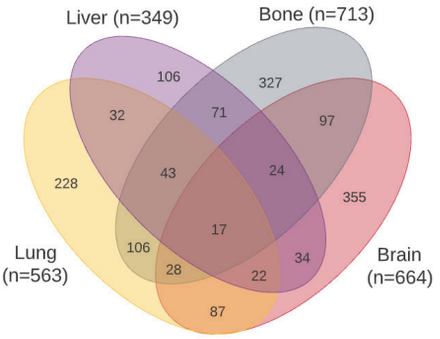

Fig. 2. Venn diagram of the distribution of metastatic sites in NSCLC patients.

Demographics and clinical characteristics

The start time was January 1, 2010, and the cut-off time was December 31, 2016. During the follow-up period, 3,221 patients (83.7%) died, and the overall median OS was 8.00 (3.00-20.00) months. Of all deceased patients, 2,935 (91.1%) died of lung cancer, and only 286 (8.9%) died from other diseases or causes.

The basic clinical characteristics are shown in Table 1. Whether the patient had distant metastasis was closely related to the patient's age, tumour primary site, tumour grade, T stage, N stage, surgery of primary site, radiation therapy, and chemotherapy ($p<0.05$).

With the increase of age, the probability of distant metastasis in lung cancer patients gradually decreased i.e., the metastasis rate for those ≤60 years old was 46.8% while those >80 years old was 33.0%. The upper lobe was the most common primary site with 2,445 individuals (approximately 63.5%), however, cancer at this site had the least metastasis (40.0%) followed by middle lobe (40.6%), lower lobe (42.1%), main bronchus (46.5%), and overlapping lesion of lung (47.5%), which had the highest risk of metastasis. With respect to tumour grade, the majority of patients with or without distant metastasis was represented as grade III (poorly differentiated) (89.1%); patients with distant metastasis were, in descending order, dedifferentiated (35.1%), poorly differentiated (42.3%), moderately

Table 1. Baseline of the demographics and clinical characteristics for patients diagnosed with NSCLC.

Characteristics	Non-metastasis	Single organ metastasis				Multiple-organ metastasis	P
		Bone	*Brain*	*Liver*	*Lung*		
Age							<0.001
≤60	578 (53.2%)	99 (9.1%)	139 (12.8%)	29 (2.7%)	66 (6.1%)	175 (16.1%)	
>60~70	740 (58.3%)	104 (8.2%)	132 (10.4%)	30 (2.4%)	69 (5.4%)	194 (15.3%)	
>70~80	641 (62.4%)	85 (8.3%)	68 (6.6%)	34 (3.3%)	58 (5.6%)	141 (13.7%)	
>80	313 (67.0%)	39 (8.4%)	16 (3.4%)	13 (2.8%)	35 (7.5%)	51 (10.9%)	
Sex							0.369
Male	999 (60.4%)	142 (8.6%)	153 (9.2%)	49 (3.0%)	93 (5.6%)	219 (13.2%)	
Female	1,273 (58.0%)	185 (8.4%)	202 (9.2%)	57 (2.6%)	135 (6.2%)	342 (15.6%)	
Primary site							0.041
Main bronchus	100 (53.5%)	16 (8.6%)	17 (9.1%)	5 (2.7%)	12 (6.4%)	37 (19.8%)	
Upper lobe	1,467 (60.0%)	193 (7.9%)	242 (9.9%)	64 (2.6%)	144 (5.9%)	335 (13.7%)	
Middle lobe	114 (59.4%)	27 (14.1%)	17 (8.9%)	1 (0.5%)	9 (4.7%)	24 (12.5%)	
Lower lobe	570 (57.9%)	86 (8.7%)	75 (7.6%)	35 (3.6%)	58 (5.9%)	161 (16.3%)	
Overlapping lesion	21 (52.5%)	5 (12.5%)	4 (10.0%)	1 (2.5%)	5 (12.5%)	4 (10.0%)	
Grade							0.005
Grade I	32 (80.0%)	1 (2.5%)	2 (5.0%)	0 (0.0%)	3 (7.5%)	2 (5.0%)	
Grade II	141 (72.7%)	12 (6.2%)	13 (6.7%)	3 (1.5%)	10 (5.2%)	15 (7.7%)	
Grade III	1,979 (57.7%)	300 (8.7%)	324 (9.4%)	97 (2.8%)	204 (5.9%)	526 (15.3%)	
Grade IV	120 (64.9%)	14 (7.6%)	16 (8.6%)	6 (3.2%)	11 (5.9%)	18 (9.7%)	
T stage							<0.001
T0	0 (0.0%)	1 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
T1	435 (79.2%)	33 (6.0%)	36 (6.6%)	7 (1.3%)	10 (1.8%)	28 (5.1%)	
T2	718 (62.8%)	97 (8.5%)	128 (11.2%)	36 (3.1%)	35 (3.1%)	129 (11.3%)	
T3	520 (55.1%)	86 (9.1%)	90 (9.5%)	25 (2.6%)	76 (8.1%)	147 (15.6%)	
T4	478 (48.5%)	84 (8.5%)	75 (7.6%)	29 (2.9%)	101 (10.2%)	219 (22.2%)	
Tx	121 (53.5%)	26 (11.5%)	26 (11.5%)	9 (4.0%)	6 (2.7%)	38 (16.8%)	
N stage							<0.001
N0	909 (74.0%)	65 (5.3%)	89 (7.2%)	20 (1.6%)	53 (4.3%)	93 (7.6%)	
N1	218 (61.4%)	35 (9.9%)	35 (9.9%)	9 (2.5%)	18 (5.1%)	40 (11.3%)	
N2	832 (51.5%)	158 (9.8%)	175 (10.8%)	54 (3.3%)	107 (6.6%)	288 (17.8%)	
N3	259 (47.5%)	52 (9.5%)	46 (8.4%)	17 (3.1%)	48 (8.8%)	123 (22.6%)	
Nx	54 (50.9%)	17 (16.0%)	10 (9.4%)	6 (5.7%)	2 (1.9%)	17 (16.0%)	
Surgery of primary site							<0.001
No	1,776 (53.5%)	320 (9.6%)	341 (10.3%)	106 (3.2%)	222 (6.7%)	556 (16.7%)	
Yes	496 (93.9%)	7 (1.3%)	14 (2.7%)	0 (0.0%)	6 (1.1%)	5 (0.9%)	
Radiation therapy							<0.001
No	1,112 (65.2%)	120 (7.0%)	67 (3.9%)	73 (4.3%)	151 (8.9%)	182 (10.7%)	
Yes	1,160 (54.1%)	207 (9.7%)	288 (13.4%)	33 (1.5%)	77 (3.6%)	379 (17.7%)	
Chemotherapy							<0.001
No	1,073 (61.7%)	114 (6.6%)	181 (10.4%)	47 (2.7%)	93 (5.3%)	231 (13.3%)	
Yes	1,199 (56.8%)	213 (10.1%)	174 (8.2%)	59 (2.8%)	135 (6.4%)	330 (15.6%)	

differentiated (27.3%), and well differentiated (20.0%). Regarding T and N stage, cancer staging was positively correlated with the probability of metastasis (except T0). Those who underwent surgery at the primary site had an extremely low metastasis rate (6.1% only). Patients with distant metastasis received more radiation therapy and chemotherapy than those without metastasis.

Survival analysis

Table 2. The median OS of the NSCLC patients with different metastatic sites.

Metastatic sites	Median OS (months)	Patients alive at the cut-off time	95% CI*	
			Lower bound (months)	*Upper bound (months)*
No	13.00 (5.00-41.00)	546 (24.03%)	12.04	13.96
Lung	6.00 (2.00-17.00)	23 (10.09%)	4.62	7.38
Liver	5.00 (2.00-13.00)	6 (5.66%)	3.56	6.44
Bone	5.00 (2.00-11.00)	18 (5.5%)	4.38	5.62
Brain	4.00 (2.00-8.00)	16 (4.51%)	3.47	4.53
Multi-organ	3.00 (2.00-7.00)	19 (3.39%)	2.59	3.41

*95%: confidence interval for the median OS.

As shown in Table 2, the median OS of patients without distant metastasis was 13 months, which is much higher than that of patients with distant metastases. Among patients with distant metastasis of lung cancer, the median OS of patients with lung metastasis was the highest (6 months), followed by liver metastasis and bone metastases, which were 5 months. The median OS of patients with brain metastasis and multiple-organ metastases was the worst with 4 months and 3 months, respectively.

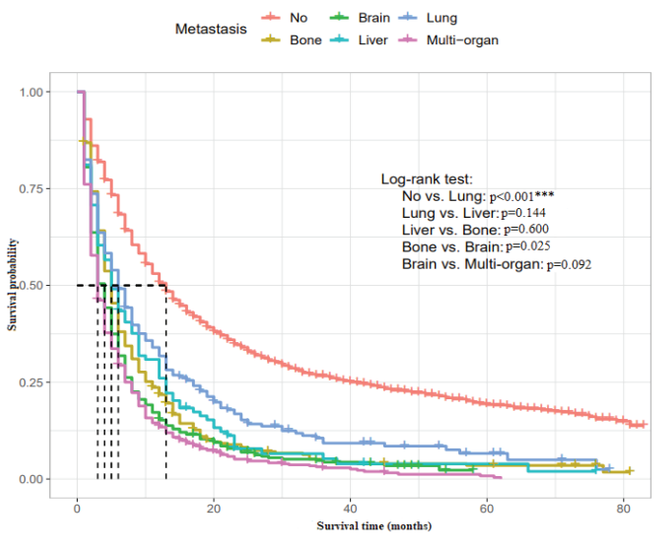

Fig. 3. Kaplan-Meier curves of the NSCLC patients without metastasis or with different metastatic sites.

It can also be seen from Fig. 3 that the prognosis of patients with NSCLC in descending order is without metastasis, lung metastasis, liver metastasis, bone metastasis, brain metastasis, and multiple-organ metastases. According to the result of the Log-rank test, the difference between the survival curves of patients without metastasis and patients with lung metastasis, as well as between bone metastasis and brain metastasis was statistically significant ($p<0.001$ and $p=0.025$, respectively).

Discussion

In recent years, with the advancement of new medical technologies, the treatment of lung cancer has rapidly developed and the OS of NSCLC patients has been significantly prolonged. However, most patients with lung cancer are at an advanced stage when they are first diagnosed and may have metastases in different sites. The process of distant metastasis of lung cancer is complex; the cancer cells leave the primary tumour and invade the blood and lymphatic system until the tumour cells grow in the distance with each step closely related to biological characteristics [6]. There are many types of metastases in advanced NSCLC patients such as single lesion, single organ, multiple lesions, and multiple organs. In this study, we mainly compared the OS of patients with lung metastasis, brain metastasis, bone metastasis, liver metastasis, and multiple-organ metastases in their medical history.

From the entire medical history of the lung cancer patients in this study, the median OS of patients without distant metastasis reached 13 (12.04-13.96) months, which was significantly higher than that of patients with distant metastases.

Among patients with distant metastasis, the median OS of patients with lung metastasis is the longest, reaching 6 (4.62-7.38) months. The prognosis is good, which may be related to the large respiratory reserve function of humans.

Following lung metastasis, the median OS of patients with liver metastasis is 5 (3.56-6.44). In contrast, R. Kitadai, et al. (2020) [7] revealed that the median OS of patients with advanced liver metastasis was 3.12 (1.71-9.03). The prognosis of patients with liver metastasis was better than those with bone metastasis. This may be related to rapid progress in the treatment of liver metastasis in recent years, and the treatment effect continues to improve.

The median OS of patients with bone metastasis was also 5 (4.38-5.62) months. Patient survival was affected by many factors such as single bone metastasis or multiple bone metastases, whether it was combined with pathological fracture, and whether it was combined with metastasis of other sites. H. Rief, et al. (2014) [8] found that the 6-month and 12-month OS of patients with single bone metastasis were 76.7 and 47.2%, respectively, and their OS was significantly higher than that of patients with other metastases by 60.0 and 34.0%, respectively. In general, patients with multiple bone metastases and with pathological fractures had poor OS.

Brain metastasis had the worst prognosis among single-organ metastases of NSCLC, with a median OS of only 4 (3.47-4.53) months. Previous studies [9, 10] have found that the factors affecting the survival of patients with brain metastasis included age, physical status, metastasis interval time, number of metastases, treatment methods, course of therapy, brain metastasis symptoms, extracranial metastases, gene mutations, programmed death receptor-1, etc. Patients with multiple organ metastases had the worst prognosis, with a median OS of 3 (2.59-3.41) months. Similar to previous research data [11], distant metastases of NSCLC were dominated by multiple organ metastases (64.4 vs 35.6%), and patients with multiple organ metastases generally had a higher tumour burden than single-organ metastasis, and their prognosis was relatively poor [12].

As mentioned above, distant metastasis suggests that patients with lung cancer have a poor prognosis, and there are many influencing factors for its occurrence. It can be seen from Table 1 that age was inversely proportional to the probability of distant metastasis. This may be because younger patients have good physical fitness, good tolerance to various treatments, and long OS time, thus, the probability of distant metastasis in the medical history increased. Same as previous clinical experience, the worse the degree of differentiation, the worse the T stage and the N stage, and the more likely the patient to develop distant metastases.

Due to the poor prognosis and many risk factors of distant metastasis of NSCLC, research on the treatment of metastasis of different organs has progressed rapidly in recent years and the prognosis has gradually improved. NSCLC patients with metastatic disease require systemic treatment. Before immunotherapy was commonly available, a platinum doublet with either carboplatin or cisplatin with gemcitabine, vinorelbine, or taxanes was widely used as the standard treatment. After the introduction of chemoimmunotherapy, the treatment landscape of NSCLC has changed significantly [13].

M. Tönnies, et al. (2012) [14] stated that patients with solitary pulmonary metastasis (outside of the tumour-bearing lobe) and otherwise operable NSCLC may benefit from surgical intervention comprising resection of the primary tumour, lymphadenectomy, and resection of the solitary pulmonary metastasis. Also, three-dimensional radiotherapy for metastases is relatively effective.

For NSCLC patients with liver metastases, M. Reck, et

al. (2019) [15] reported that the survival of patients treated with atezolizumab plus bevacizumab plus carboplatin plus paclitaxel had better improvement than those given bevacizumab plus carboplatin plus paclitaxel. P.C. Tumeh, et al. (2017) [16] proposed that liver metastatic patients with NSCLC who had been treated with pembrolizumab were associated with reduced responses and progression-free survival, and liver metastases were associated with reduced marginal CD8 + T-cell infiltration, which provides a potential mechanism for this outcome.

Bone metastasis was associated with a significant increase in skeletal-related events including pathological fractures, hypercalcaemia, spinal cord injury, and uncontrolled pain requiring bone surgery and/or radiotherapy [17]. Currently, there are opioid analgesic treatments, zoledronic acid, and ibandronic acid, while some patients are treated with radiation therapy and a small number of patients are treated with surgery.

Regarding brain metastases in NSCLC, the former primary treatment selection included surgical resection, stereotactic radiosurgery, and whole-brain radiation therapy. With the finding of targetable molecular drivers and the increase of an enormous number of tyrosine kinase inhibitors, treatments have become complicated [18].

There were also several limitations in the study. First, selection bias in retrospective data could not be entirely avoided. Second, we were unable to obtain more specific data such as laboratory results and treatment drugs. Finally, if a patient moved to a different part of the United States where SEER data was not gathered, patient follow-up may have come to an end.

Conclusions

In summary, this study suggested that the occurrence of distant metastases of NSCLC patients had a great impact on the prognosis. There were significant differences in the prognosis of different metastatic sites and the order of their OS from high to low was: no metastasis > lung metastasis, liver metastasis, bone metastasis > brain metastasis, multiple organ metastasis. For patients diagnosed with NSCLC, early assessment of the systemic condition and clear staging are conducive to a more accurate prognosis.

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COMPETING INTERESTS

The authors declare that there is no conflict of interest regarding the publication of this article.

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